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During the third year of this project, the components of a model of breast cancer screening were coded and verified, and validation begun. Supporting code for a graphical Basic User Interface was put in place. Groundwork was done in preparation for simulating multicohort populations, in collaboration with researchers from NCI. Draft parameter sets were derived for disease biology, screen test characteristics, survival, and costs, and those for disease biology and survival were then refined and finalized. The fourth year of the project will be devoted primarily to validation and sensitivity analyses, with additional effort on refinement of parameter sets and integration with the graphical user interface.

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Nicole Urban 9/19/97

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Annual Report for Grant DAMD17-94-J-4237

August 22, 1996 - August 21, 1997
Year 03

Development of a Stochastic Model of the Cost-Effectiveness of Promoting Breast Cancer Screening

Nicole Urban, ScD
Principal Investigator

Table of Contents

Introduction

The purpose of this four-year project, funded in August 1994, is to identify an efficient strategy for reducing breast cancer mortality through breast cancer screening. To identify such a strategy, the trade-off between the frequency of screening among participants and the promotion of participation among underusers will be investigated. Ways to improve the effectiveness of screening in women aged 40-49 will be investigated, using new biomarkers and detection modalities, and the relative cost-effectiveness of various interventions to promote the use of regular breast cancer screening among women aged 50-80 will be investigated. A comprehensive stochastic simulation model of the effectiveness and cost-effectiveness of breast cancer screening will be developed, and its key parameters estimated.

Body

Year 03 was spent creating the algorithms needed to simulate breast cancer screening and implementing those algorithms using the programming language Gauss. Thirty-five separate components produce a complete simulation of disease, screening efforts, survival and costs (see **Figure 1** and **Table 1**). Supporting code integrates the microsimulation model with a database of model parameters external to the model and with a post-processing program that summarizes and presents model results. Year 03 was also spent constructing model parameters (see **Table 2**). Data sources include the National Cancer Institute's (NCI's) Surveillance, Epidemiology and End Results (SEER) program, Dr. Urban's Mammography Tumor Registry, and the scientific literature.

We collaborated with NCI investigators on a project entitled POPSIM, the goal of which is to extend existing microsimulation models to allow simulation of multicohort populations. Matt Gable, Lauren Clarke, and Ray Cha, the builders of breast, ovarian, and prostate cancer models, respectively, traveled to NCI headquarters in May, 1997 to discuss the POPSIM project with collaborators, Drs. Eric Feuer and Julie Legler. Progress has been made on collecting cohort-specific demographic and disease parameters for the US population, solving conceptual problems in modeling populations, and joint software development. Drs. Feuer and Legler also traveled to the Hutchinson Center in July, 1997, for further discussion of the joint project.

Collaboration with researchers from the University of Washington, including Dr. Ben Anderson, a surgeon specializing in breast cancer, and Drs. Mariann Drucker and Connie Lehman, radiologists, continued in Year 03 with provision of expert advice on tumor biology and mammography.

Mr. Gable participated in the "Workshop on Cost-Effectiveness in Health and Medicine" in November, 1996 at the National Institutes of Health (NIH) in Bethesda, Maryland. The workshop provided exposure to the conclusions of a consensus panel convened by NIH to determine standard practice in cost-effectiveness analysis.

Details of the work completed in Year 03 are described below:

Disease is modeled via tumor size and an assumption of exponential growth (see **Figure 2**). Tumor size at various events, including clinical diagnosis, metastasis, invasion, and first detectability, is assigned from parameter distributions derived from data sources such as SEER. Coupled with simulation of tumor growth, sizes at events indicate a woman's age at events and, conversely, important tumor characteristics at the time of screen tests.

Screen test results are calculated based on tumor characteristics and breast density at the time of the test. A tumor is detected if a test occurs after the tumor has reached detectable size. False positive test results are checked for at random for each screen test. Size at detectability and probability of false positive results are both affected by breast density, which may change over the life of a woman. Timing of screen tests may be varied at will: the sample output shown in **Figure 3** is from a simulation of biennial screen tests given from ages 50 to 80. The output displays an initial increase in incidence as prevalent cases are found and a reduction in incidence after several years of screening.

Survival is modeled by generating cancer survival time from age- and stage-specific relative survival curves derived from SEER data. A separate age at death from causes other than cancer is generated from an adjusted life table. For clinical detection, survival time is added to age at diagnosis to give age at death. For screen detection, survival time is added to age at screen detection plus lead time to give another age at death. These ages at death from cancer are compared to the age at death from other causes to determine actual age and cause of death.

Costs of screen tests and any additional procedures resulting from false positive findings are assessed and discounted at various rates (0, 3 and 5% are standard). Treatment costs vary by stage of diagnosis and are assessed by a phase-of-treatment system, in which costs are high during the initial year after diagnosis, decline to a maintenance level thereafter, and rise again in the terminal period of the last six months before death. They are likewise discounted at various rates.

Code to support integration with an external Basic User Interface includes a data-loading procedure that allows parameters to be changed without entering the microsimulator code, output procedures that allow subsets of the data created by the model to be exported for later analysis, again without entering the microsimulator code, and a system of generic labels that allow data from our breast, ovarian and prostate models to be handled by the same external software. This supporting structure is important to the POPSIM project, in which many more inputs and outputs must be tracked for a full population than for a single cohort.

Verification of the model code has been conducted to confirm that the model functions as expected. Output from most variables has been processed to replicate the input parameters, and programming errors corrected where necessary so that outputs match the inputs as expected. The behavior of the model has been examined for plausibility where quantitative checks have not yet been done or would require validation, and inconsistencies corrected where needed. Initial validation against a Dutch clinical trial found nearly exact agreement, but much more thorough validation remains to be done before confidence may be placed in the model's results.

Conclusion

Summary of Year 03

During the third year of this project, the components of the model of breast cancer screening were coded and verified, and validation begun. Supporting code for a graphical Basic User Interface was put in place. Draft parameter sets were derived for disease biology, screen test characteristics, survival, and costs. Some parameter sets for disease biology and survival were then refined and

finalized. Groundwork was done on the integration of the breast cancer model into POPSIM, in collaboration with researchers from NCI, in preparation for simulating multicohort populations.

Plans for Year 04

The next year of the project will see the completion of required parameter sets and validation and sensitivity testing of the model. Important issues in parameter development include a quantification of the size range at which breast tumors first become detectable, a more precise accounting of costs incurred during a false positive mammogram and during treatment, and possible refinement of breast density parameters.

A poster presentation on the model is planned for November, 1997 at the "DOD Breast Cancer Research Program: An Era of Hope" conference. The poster will present preliminary results and sensitivity analyses.

We continue to collaborate with investigators in the Netherlands and at the University of Washington, including scientists investigating the tumor biology of breast cancer at the molecular level. Use of the model to evaluate the potential usefulness of new tumor markers is planned.

Microsimulation Model of Breast Cancer Screening

Matt Gable 5/29/97

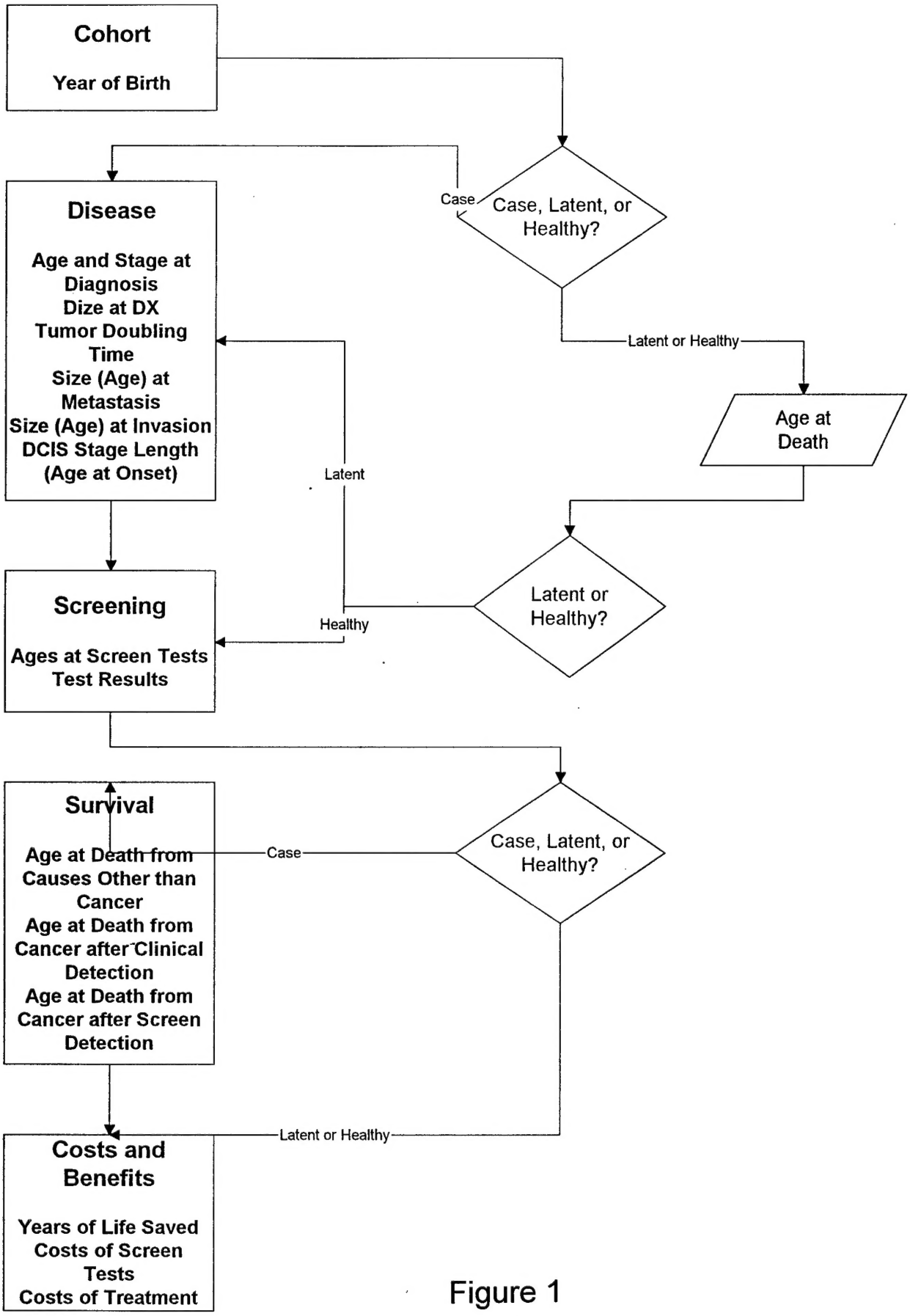


Figure 1

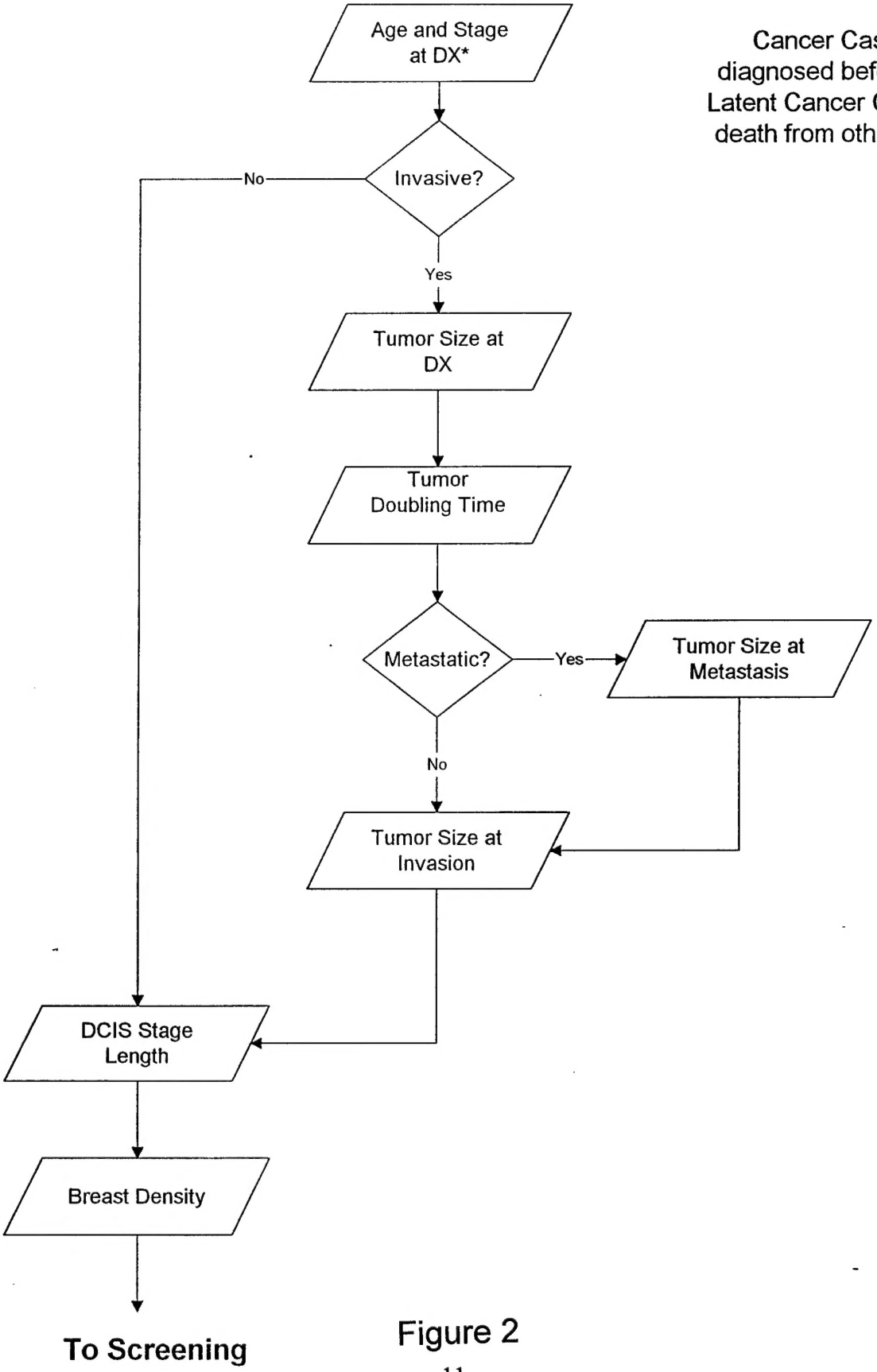
Table 1: Parameters used in the microsimulation model of breast cancer screening.

Parameter	Description
initseed	initial random number seed. must be an integer from 1 to 2,147,483,647
wtlatent	weighting factor for latent cancer cases. 1 latent case is generated for each "wtlatent" latent cases in the population simulated
wthealth	weighting factor for healthy women. 1 healthy woman is generated for each "wthealth" healthy women in the population simulated
youngest	youngest age at which cancer cases are generated
oldest	oldest age to which individuals can survive
Nsubj	# subjects per run, cases + healthy
DTBo, DTB1	coefficients in the regression of ln(doubling time) on ln(age at DX) using Peer et al (1993) and assuming average ages in categories of 45, 60, 75
invsizec	size at invasion (cm). Must be less than any size at DX or metastasis
DCISrate	lambda parameter for exponential distribution of DCIS stage length
minonset	cutoff age for extension of tail of exponential DCIS dist
sstart	age at which screening starts
s_end	age at which screening ends
schdmeth	method for scheduling screens: 1 = first-order Markov chain 2 = fixed-interval, all women screened
scrpct	proportion of women ever screened in their lives. Used in Markov chain
secscpct	of women receiving a screen, % return for a second screen. Markov chain
s_interv	minimum time between screens, in years.
specmm	specificity of mammography, = 1 - %false +
undetmm	% of cancers undetectable by mammography (lobular, etc)
followup	length of followup to identify false negative test results, in years
mamcost	cost of a mammogram, in dollars
biopcost	cost of a biopsy, in dollars
discount	discount rate
refage	reference age for which present value is calculated during discounting
refyear	reference year for which present value is calculated during discounting
birthyr	year of birth, with decimal places. Presently a constant (a cohort).
lifetabl	hazards for all-cause mortality
comodist	hazards for competing mortality
DCIShaz	hazards for DCIS
earlhaz	hazards for early-stage invasive cancer
latehaz	hazards for late-stage invasive cancer
DTdist	age-specific tumor volume doubling time
sizeearl	age- and early-stage specific size at clinical detection
sizelate	age- and late-stage specific size at clinical detection
metssize	age-specific size at metastasis
sizedet	age-specific size at earliest detect
brdenpr	breast density transition probs
firstscd	age at first screen in Markov chain
secscdst	time first->sec scr in Markov chain
schddist	screen time matrix in Markov chain
survnoca	survival, no cancer
survdcis	survival after DCIS
survearl	survival after early stage cancer
survlate	survival after late-stage cancer
phscosts	costs of treatment by phase of survival

Table 2: Components (Gauss procedures) in the microsimulation model of breast cancer screening

Component	Description
Cohort:	
brdensp3	assign ages at transitions in breast density
Disease:	
DXp	assign age and stage at clinical detection
DXsizep	find size at clinical diagnosis conditional on stage
DTregrp	assign tumor doubling time using continuously varying age
metsizep	calculate size at metastasis conditional on age and < DXsize
invsizep	size at invasion (presently a constant)
metsagep	calculate age at metastasis, in years
invagep	calculate age at invasion, in years
onsetp7	assign age at onset based on exponential distribution of DCIS stage length (constant risk of invasion)
Screening:	
detsizep	assign size at earliest detectability <= DXsize
Markov2p	schedule screen tests via Markov chain
fixedintp	schedule screens at a fixed interval
resultsbydetsizep	find results of screen tests
TPp	identify true positives
TNp	identify true negatives, defined as no clinically detected cancer within followup period
TNtestp	identify negative test when cancer not present
FPp	identify false positives
Fnegp	identify false negatives, defined as clinically detected cancer within followup period
Fnegtestp	identify negative test when cancer is present
Survival:	
clinstgp	find stage at clinical detection
scrnstgp	stage at screen detect
nc_ageatdeathp	survival time from other causes, measured from diagnosis
cl_ageatdeathp	survival after clinical detection
sc_ageatdeathp	survival after screen detection
agecausep	find age and cause of death
YLSp	determine years of life saved due to screening
Costs:	
costtestp	find costs of screen tests
phasedtreatmentcostp	find costs of treatment using 3 cost phases
Lmortp	assign age at death for latent cancer cases
mortp	assign age at death for cancer-free women
Lscrnstgp	stage at screen detect for latent cancer cases
Hresultsp	determine test results for cancer-free women
HTNp	identify true negatives for cancer-free women
HFPp	identify false positives for cancer-free women
Hcosttestp	find costs of screen tests for cancer-free women

Disease Module



Cancer Cases are diagnosed before death, Latent Cancer Cases after death from other causes.

Figure 2

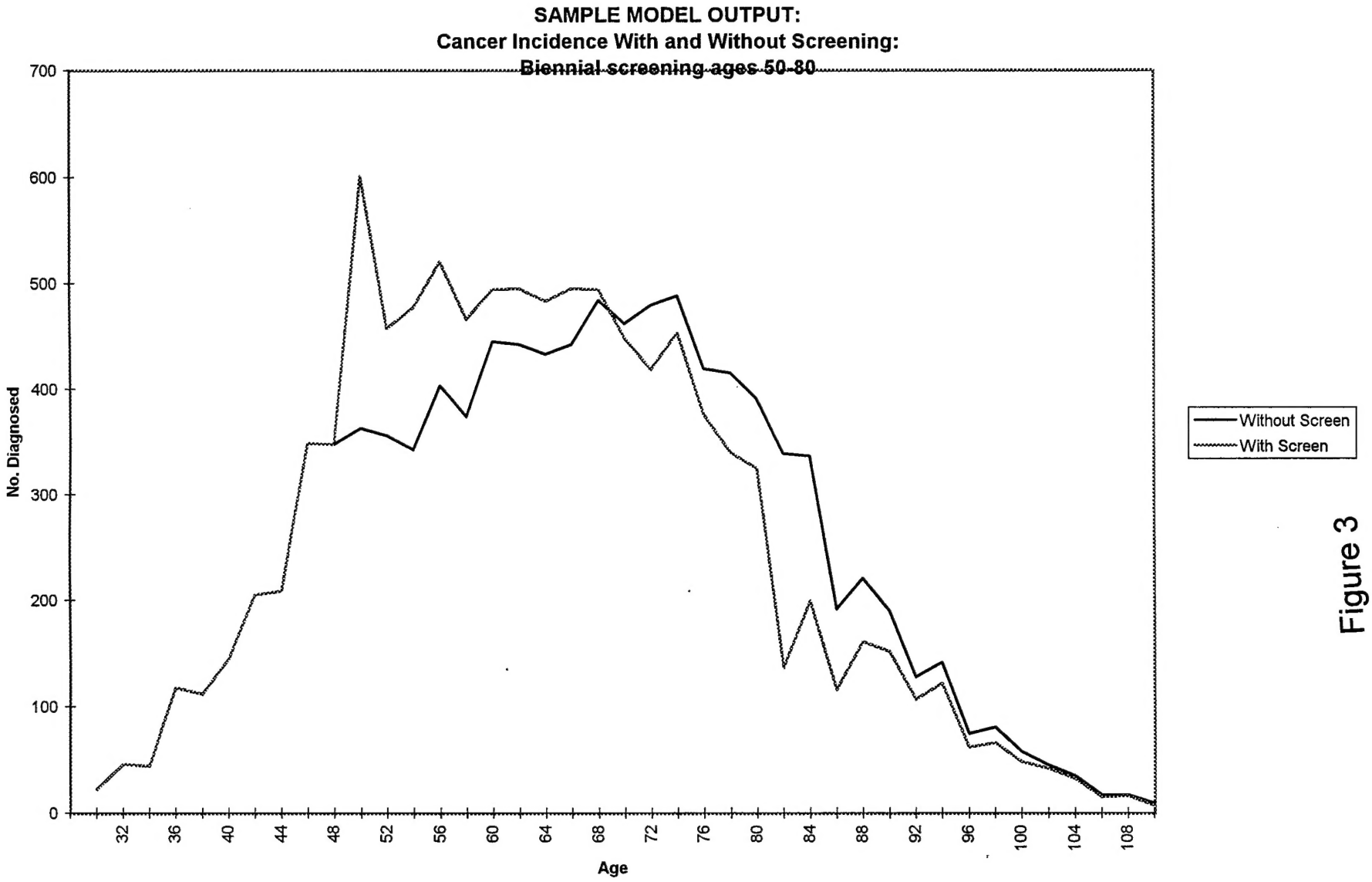

SAMPLE MODEL OUTPUT:
Cancer Incidence With and Without Screening:
Biennial screening ages 50-80
No. Diagnosed
Age
Without Screen
With Screen
0
100
200
300
400
500
600
700
32
36
40
44
48
52
56
60
64
68
72
76
80
84
88
92
96
100
104
108

Figure 3

Survival Module

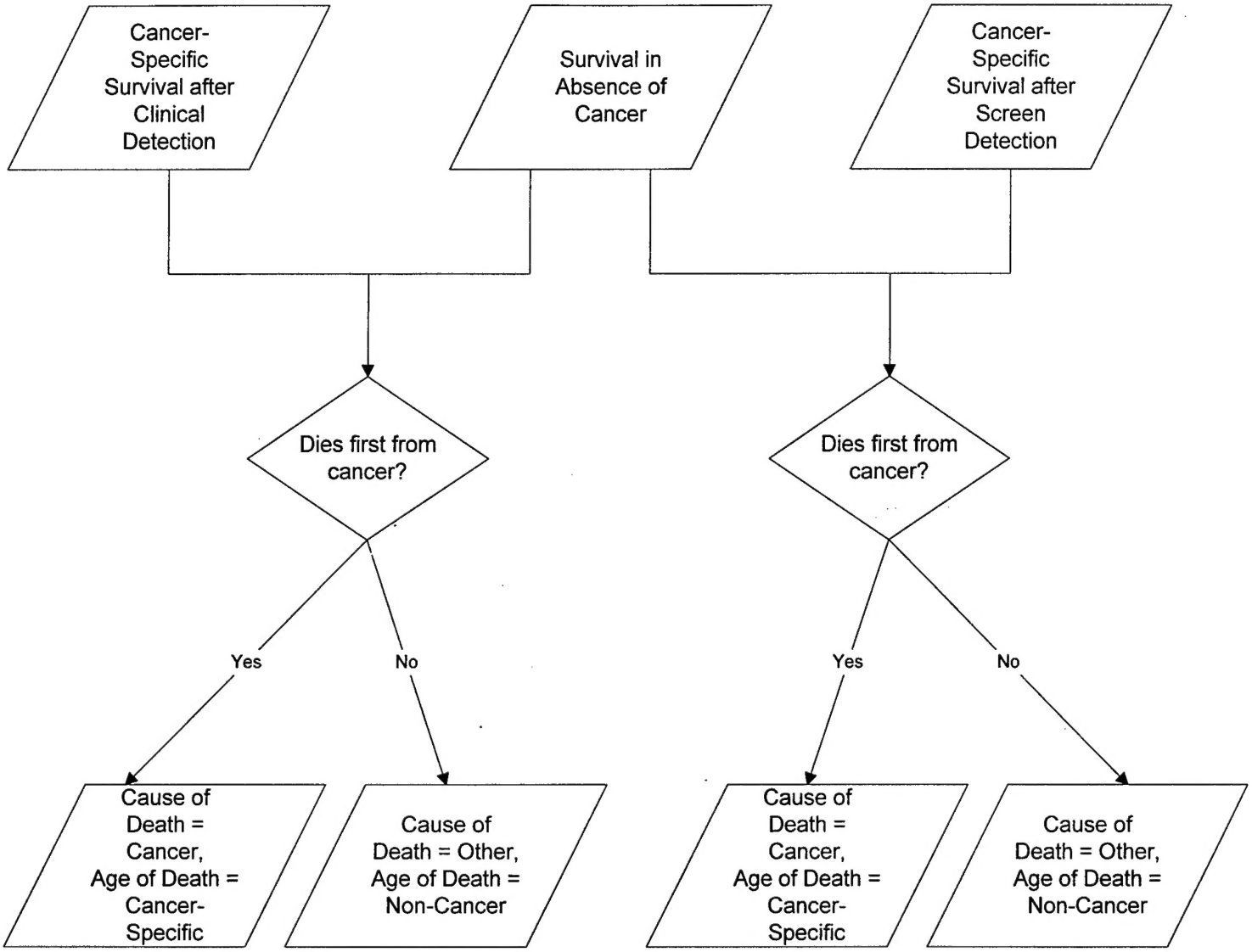


Figure 4